The critical relationship between compliance and the management of infectious diseases

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INTRODUCTION

Compliance with anti-infective drugs is possibly the most important issue that will face communicable disease physicians in the new millennium. Non-compliance is common among patients prescribed self-administered medication and carries heavy costs for the individual, the health provider and public health. For the individual, non-compliance may result in a reduction of therapeutic benefit, drug resistance, drug toxicity and the greater likelihood of disease progression. For the health provider the cost is enormous in terms of wasted drugs and the cost of treating additional morbidity. It has been estimated that hospitalization due to non-compliance accounts for 11.7% of all healthcare expenditure in the USA [1]. Moreover, with communicable diseases there are important public-health implications, including failure to eliminate the infection, increased drug resistance in the community and prolonged infectivity.

WHAT IS COMPLIANCE?

Compliance can be defined as the extent to which a person's behavior (in terms of taking medications, following diets or executing lifestyle changes) coincides with medical or health advice. It is most widely used to describe the degree to which patients follow the regimen of medicine-taking recommended by their doctor and therefore has attributes of both quantity and time. The term compliance has been criticized on the ground that it disregards the autonomy of the patient. 'Adherence', which connotes patient choice in following the prescribed regimen, is often used in preference. In this article, the terms compliance and adherence will be used interchangeably.

Types of non-compliance

Compliance is not a simple matter of obeying instructions. Non-compliance exists on different levels and is expressed in different ways. Non-compliance may be intentional, based on reasoned decision-making influenced by the patient's views on drugs and his or her own condition [2], or it may be unintentional, arising from factors such as depression, lack of coping, disorganized lifestyle, communication problems and lack of information. The most commonly observed forms of non-compliance are: (1) failure to have the prescription dispensed, (2) omission of doses, (3) errors of dosage, (4) deviations in dose timing and (5) early cessation of the drug [3]. An essential factor in evaluating compliance for different treatments is the threshold of therapy needed to maintain the effectiveness of the regimen (i.e. how much compliance is enough). For example, triple combination antiretroviral therapy for HIV infection necessitates a high degree of compliance to suppress viral replication. In contrast, high-dosage oral contraceptives can maintain contraceptive efficacy even with lapses in dosing of several days.

METHODS FOR MEASURING COMPLIANCE

Patient self-reports

History-taking, diaries, questionnaires and self-report scales have all been used to obtain patient reports of

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compliance. These patient self-reports have been shown to greatly overestimate adherence [4].

Pill counts

In this method the pill bottle is recovered at the end of a course of medicine and the number of remaining pills counted to measure drug underuse or overuse. This technique tends to overestimate adherence, and similar pill count results may be obtained from very different types of non-compliance. Patients often fail to bring their medication with them at the time of their clinic visit or may empty their pill bottles rather than admit non-compliance. While far from satisfactory, pill counts continue to be almost universally used in drug trials [5].

Pharmacologic markers

This method involves the addition of a low-dose pharmacologic marker to the medication under study. A measure of adherence is obtained by measuring the level of the pharmacologic indicator in the blood or in urine. Low-dose phenobarbitone has been widely used as an indicator [6]. This method of measuring adherence has been shown to be both accurate and reproducible.

Monitoring of the primary therapeutic agent

In this method, adherence is assessed by measuring the plasma or urine concentration of the primary therapeutic agent. It is highly dependent on pharmacokinetics, and drugs with short half-lives, such as penicillin, are unsuitable for this method. Biochemical validation is not feasible with many compounds for which assays are not readily available. The results of blood and urine tests are influenced by variable drug absorption, metabolism and clearance. This method is problematic, because the levels taken at the time of measurement give no indication of blood levels between measurements, especially for short-acting drugs.

Electronic monitoring

Electronic monitoring devices have been developed to measure adherence to medication. These devices record the times and dates when the medication bottle has been opened and are unique in being able to reveal accurately the temporal patterns of dosing. The use of this method has revealed drug holidays (multiday lapses in dosing) and 'white-coat compliance' [7] (the tendency for usually poor compliance to improve in the day or two prior to a scheduled visit to the physician) to be common. In interpretation of the data, it is assumed that medication removed from its container is actually ingested. Although this may not be true, it would require persistent adherence to the dosing schedule for a patient to fake good compliance, as the micro-circuit records the time of each opening. Electronic monitoring devices exist for medication presented as loose tablets, capsules, tablets or capsules in blister packs, inhaled medication and eye drops.

Electronic monitoring and pharmacologic markers are complementary methods, as together they enable accurate measurement to be made of dose taking and dose timing.

FREQUENCY OF NON-COMPLIANCE

While there is a consensus that non-compliance is an important problem, different approaches to measurement, to the definition of non-compliance and to endpoint assessments mean that estimates of the size of the problem vary widely. Estimates of poor compliance range from 20% to 80% [8]. A review of methodologically rigorous studies concluded that compliance with different long-term medication regimens tended to converge to approximately 50% [9].

FACTORS AFFECTING COMPLIANCE

Factors relating to the drug regimen

The complexity of the treatment regimen has a significant impact on compliance [10]. Reliable measures indicate little difference in compliance between once- and twice-daily regimens, but considerably higher rates of omitted doses and errors in dose timing with three times a day or four times a day dosing [11,12]. Long-acting drugs, or drugs that can be administered once daily, can be important in helping to achieve compliance. However, once-daily dosing has a major problem. Unless the once-daily dose has a long plasma half-life, if there is a missed dose it will result in a low serum drug concentration for an 18–24-h period. Continuity of therapeutic action is best ensured when the prescribed interval between doses is substantially shorter than the duration of the drug action. The number of drugs taken concurrently also affects compliance [13]. Some studies suggest that frequency of dosing is a more important determinant of compliance than the number of different drugs prescribed [14,15].

There is evidence that the level of non-compliance rises as the duration of therapy increases [16]. In a study of patients with otitis media given a 10-day course of oral penicillin, up to 50% were found to be non-compliant by day 3, rising to 70% by days 6–7 [17]. Unpleasant side effects can affect compliance. In an early study of *p*-aminosalicylic acid for tuberculosis [18], in which a third of patients experienced nausea

and diarrhea, less than 50% of patients complied with their regimen. In patients with HIV infection, side effects, including leukopenia, anemia and gastrointestinal upset, have been shown to lead to decreased adherence and treatment cessation [19].

Patient-related factors

Factors such as age, gender, educational level, socioeconomic status and personality traits have been shown to influence compliance. However, the factors most strongly associated with improved compliance are patients' health beliefs, social support, patient understanding of the prescribed therapy and the doctor–patient relationship. These are clearly connected by the central roles of communication and reinforcement.

Patients' beliefs about illness and medication are strong determinants of seeking care and accepting therapy. Compliance is strongly influenced by the patient's perception that their wellbeing is at threat from the disease and that the benefits from prescribed therapy outweigh perceived barriers to compliance with it (e.g., drug cost, side effects and complexity of the regimen). Lay beliefs about illness and medication may differ quite markedly from those held by health professionals. This leads to difficulties in communication, which can result in confusion, frustration and non-compliance [20]. This may be particularly true where the patient and provider have different cultural or ethnic backgrounds. Frequently, medicine is aimed at the disease process and not at the immediate alleviation of symptoms. This differentiation between symptoms and disease process is not widely understood by patients, and leads to non-compliance and early cessation of treatment, particularly with antibiotics. A Europe-wide study of patients' attitudes to the use of antibiotics for respiratory tract infection showed that 81% of respondents expected symptoms to improve after 3 days' treatment; for 87%, feeling better justified stopping the course of antibiotics [17]. This study revealed differences between countries in how antibiotics were perceived. Respondents from Belgium, Turkey and Italy showed particular concern that antibiotics could undermine natural immunity, particularly in children. Side effects, addiction, dependency and the development of resistance were also cited as concerns.

Major causes of poor compliance include the failure to understand the importance of the drug therapy and the potential consequences of not using the medication according to instructions, and the failure to understand the instructions given. A good understanding of the prescribed therapy and knowledge about the reasons for taking the drug and the complexity of the regimen have been shown to improve adherence significantly with anti-HIV drugs [21,22]. Clear explanation of the timing of doses is needed. A study to assess the relationship between the prescriber's instructions and the patient's adherence to a prescribed 5-day antibiotic schedule showed that 99.6% of patients took the correct number of doses but only 32.6% took their medication within 1 h before or after the optimal 12-hour interval [23]. In another study of how patients interpret prescription instructions, 36% of patients interpreted 'tetracycline, 250 mg every 6 h' to mean every 6 h around the clock for a total of four doses each day. About 25% of the patients divided the time they were awake and took only three doses throughout the 24-h period [24].

Written instructions which are clearly explained by a doctor, pharmacist or nurse can improve compliance. Aids such as timed pill dispensers, alarm clocks, multicompartment containers and dose checklists for complex regimens have also been shown to be effective. Perhaps more fundamental is the need for health professionals to use their verbal communication skills and knowledge to tailor the treatment plan as much as possible to the patient's lifestyle and circumstances. The health professional and patient must work together to identify routines so that medication is administered at times that correspond to some of the patient's regular activities. Various aspects of the relationship between patients and health professionals have been identified as being important to compliance (these include continuity of care, shared beliefs regarding illness and medication [20] and patient satisfaction with care provided [25]). Pharmacists, nurses and doctors have figured prominently in successful strategies to improve adherence but there is very little research evaluating the comparative effectiveness of different healthcare professionals on compliance.

COMPLIANCE AND CONCORDANCE

Non-compliance is a phenomenon 'so widespread that it might well be considered normal behaviour' [26]. As such, when explanations are sought for treatment failure, it must be considered alongside factors such as pharmacologic non-response and poor bioavailability. The lack of rigorous study design in compliance research makes evaluation of interventions to improve compliance problematic. However, it would appear that two of the most important factors to ensure good compliance are clear instructions to the patient (linking dosing to some regular feature of the patients' daily routine) and the simplest regimen consistent with continuous efficacy.

A recent Royal Pharmaceutical Society Working Party report from the UK [27] concluded that for patients to be enabled to take medicines to best

effect, it is necessary to rethink the patient/prescriber consultation. The concept of 'concordance' is mooted as an alternative to 'compliance'. Concordance is based on the notion that the work of the prescriber and the patient is a negotiation between equals and that therefore the aim is a therapeutic alliance between them. How far this therapeutic alliance will be achieved in practice remains to be seen.

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SELF-ASSESSMENT QUESTIONS

Please answer true or false:

1. Once-daily antibiotic medication gives greatly superior compliance to twice-daily medication.
2. The most effective way of measuring compliance is to ask patients to bring in their pills, to count them and to compare them with the number which should have been taken.
3. Pharmacologic markers provide the most accurate measure of the timing of dosing.
4. Many of the problems of patients complying with, or adhering to, their therapy are due to the lack of understanding that the doctors have of the patients' particular situations and beliefs concerning the disease. One of the most important ways to improve compliance on long-term medication is to spend time in ensuring that patients understand the long-term benefits of their medication.
5. If you have a good standard explanation of why drugs are important, you can give this either verbally or in writing to all your patients.

6. Patients who are not compliant are rare and can be easily recognized by health professionals.

SELF-ASSESSMENT ANSWERS

1. False. There appears to be little difference in compliance between once-daily and twice-daily medications. Unless the drug has a long plasma half-life, a missed dose of once-daily medication can lead to a low serum drug concentration for an extended period.
2. False. Pill counting is one of the least effective methods of measuring compliance. It tends to overestimate adherence, especially where patients dump their medication before their clinic visit.
3. False. Pharmacologic markers provide the most accurate measurement of dose taking. Electronic monitoring is the most appropriate method to demonstrate dose timing.
4. True. This is one of the most important messages that arises from compliance research.
5. False. Verbal and written explanations may need to be adapted for particular patients, e.g. those from different cultural or ethnic backgrounds.
6. False. Non-compliance is not a deviant behavior but a common phenomenon arising from factors relating to the drug, the health provider, and the patient, and must be considered when seeking explanations for treatment failure.